Population-based study of risk of breast cancer in carriers of *BRCA2* mutation

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Summary

Background Estimates of an 80–90% risk of breast cancer for carriers of germline mutations in the *BRCA1* and *BRCA2* genes are based on studies of families at high risk of breast cancer. Risk estimates for a population are possible if the mutation status of a representative sample of that population can be assessed. In Iceland, one common founder *BRCA2* mutation occurs in 0·6% of the population. Iceland has a population-based cancer registry and a large collection of pedigrees, and estimation of cancer risk in mutation carriers is therefore possible.

Methods We studied 575 breast-cancer patients, 541 women and 34 men unselected for family history of breast cancer. Data on cancer in first-degree relatives were available from the cancer registry. Risk of cancer was estimated by comparing the history of cancer in first-degree relatives of carriers and non-carriers.

Findings 56 (10·4%) of the 541 women and 13 (38%) of the 34 men carried the 999del5 mutation. The estimated risk of breast cancer at age 50 for all female carriers of the 999del5 mutation was 17·0% (95% CI 9·1–25·9) and 37·2% (22·4–53·9) at age 70.

Interpretation The results of our population-based study show that the mean risk of breast cancer in carriers of mutation in *BRCA2* is lower than previously suggested. Individual risk assessment will, however, have to take account of family history.

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Introduction

Germline mutations in known and unknown breast-cancer susceptibility genes account for an estimated 5–10% of cases of breast cancer. The two major breast-cancer genes are the *BRCA1* gene on chromosome 17q and *BRCA2* on chromosome 13q.[1–3] Mutations in these genes are rare in the general population, but their discovery has made it possible to offer predictive genetic testing for women thought to be at risk of breast cancer. Most mutations described in each the *BRCA* genes are frameshift, non-sense, or splicing mutations that lead to premature protein truncation.[4] Carriers of mutations in the *BRCA* genes are at increased risk of breast cancer, but the magnitude of the risk is unknown, especially in the general population.

Several studies have estimated the lifetime risk of breast cancer for carriers of *BRCA* mutations.[5–11] Studies that used the Breast Cancer Linkage Consortium database estimated the risk of breast cancer at age 70 to be greater than 80% for carriers of *BRCA1* and *BRCA2* mutation.[5,6] The database included selected families with more than one member with breast cancer, who had cancer at an early age: the risk estimates from this group may not apply to carriers of *BRCA1* and *BRCA2* mutations in general. Studies of Ashkenazi Jews show that the risk associated with *BRCA1* and *BRCA2* mutations may be lower than previously published data indicate.[7,8]

Risk estimates require assessment of the mutation status of a representative sample of a population. The *BRCA* genes are large, and mutations are distributed over the whole gene, which makes large-scale screening for mutations difficult. Different mutations in the *BRCA1* and *BRCA2* genes are associated with different cancer risk.[9–11] However, certain mutations may be more common within a defined population, which makes screening of that population easier and makes it possible to estimate risk of cancer among mutation carriers. Among Ashkenazi Jews, two common founder mutations have been identified; 185delAG in *BRCA1* and 6174delT in *BRCA2*, each appearing in about 1% of this population. A third mutation, 5382insC in *BRCA1*, appears in 0·11% of this population.[12–14] The risk of breast cancer in Ashkenazi Jews who carry these three mutations was estimated by comparing the history of breast cancer in first-degree relatives of carriers and non-carriers.[7] That study group consisted of volunteers from the Jewish population in Washington DC, USA, and the estimated risk of breast cancer in mutation carriers was 56% at age 70.

The population of Iceland is small and well defined, which allows an unbiased estimation of risk of cancer among mutation carriers. Information on all cancers is available from medical records at a cancer registry in Iceland, together with pedigrees of unselected breast-cancer patients. A recurrent *BRCA2* mutation, 999del5,

	Breast-cancer cases		First-degree relatives		Cases of cancer among first-degree relatives		
	Female	Male	Female	Male	Female breast cancers	Male breast cancers	Prostate cancers
Mutation carriers	56	13	252	301	36 (14·3%)	4 (1·3%)	11 (3·7%)
Non-carriers	485	21	2156	2159	115 (5·3%)	1 (0·5%)	51 (2·4%)

Table 1: **Composition of study group**

a 5 bp deletion in exon 9, has been found in 16 of 21 Icelandic families with a history of breast cancer.[15] Studies of the Icelandic population[16,17] have shown that this mutation is found in 7·7% (95% CI 5·7–9·7%) of unselected female breast-cancer patients, and in an estimated 0·6% (0·1–1·7) of the general population. The 999del5 mutation has also been found in 40% of male breast-cancer patients in Iceland.[17] Among the Icelandic population there is no indication of other *BRCA2* mutations,[15] and only one rare *BRCA1* mutation has been detected.[18] Thus, we were able to study the effects of the 999del5 mutation on the risk of breast cancer, by comparing the risk of breast cancer in first-degree relatives of mutation carriers to the risk of breast cancer in relatives of non-carriers.

Methods

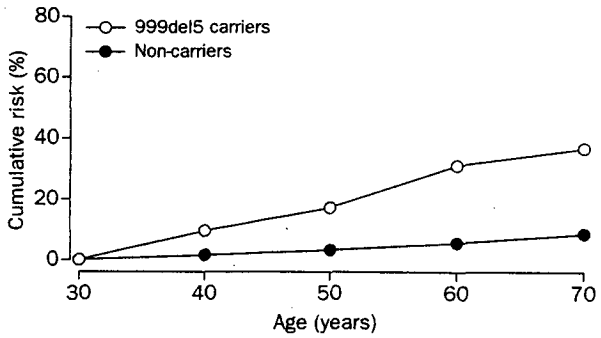
The Icelandic Cancer Registry (ICR) contains information on all cancer cases in Iceland since 1955 and all breast cancers since 1910. All data on cancer are based on medical records, and include 947 breast-cancer pedigrees.[19] We studied 575 patients with breast cancer, 541 women and 34 men. The ICR contains data on all first-degree relatives of these patients.

Tissue samples from the 541 women were collected over two periods, during which time 1214 women were diagnosed with breast cancer in Iceland as a whole. The 541 women in our study thus represent 45% of all cases of breast cancer. 72% of the 541 women gave fresh blood samples, but for 152 (28%) DNA had to be extracted from paraffin-embedded tissue. The samples were randomly collected and were unselected for family history of cancer.

In 1955–96, 34 men were diagnosed with breast cancer in Iceland.[20] Tissue samples were available from all of these cases, 19 from paraffin-embedded tissue and 15 fresh blood samples. The median age at diagnosis was 56 years for women and 67 years for men.

Data on the 541 female breast-cancer patients did not differ in terms of breast-cancer incidence, age at onset, or family history from the population-based series in the registry. Familial relationships between individuals were recorded and then personal identification was removed from the data.

BRCA2 999del5 mutation status was assessed by PCR amplification and polyacrylamide-gel electrophoresis.[15] All genetic analysis was done on coded samples.



Cumulative risk of breast cancer in female mutation carriers and non-carriers by age

Cancer risk	Relatives of male and female breast cancer patients (95% CI)		Relatives of gentoyped female patients only (95% CI)	
	By age 50	By age 70	By age 50	By age 70
Breast				
Carriers	17·0 (9·1–25·9)	37·2 (22·4–53·9)	15·4 (7·1–25·1)	35·4 (16·9–56·4)
Non-carriers	2·3 (1·6–3·1)	8·1 (6·5–9·9)	2·3 (1·5–3·2)	8·4 (6·6–10·2)
Prostate				
Carriers	1·2 (0–4·4)	7·6 (0–17·2)	..	..
Non-carriers	0	2·3 (1·2–3·4)	..	..

Table 2: **Risk of cancer in carriers of 999del5 BRCA2 mutation**

Penetrance, the conditional probability of cancer in a mutation carrier, was estimated by comparing the history of cancer among the set of first-degree relatives of carriers with that among the first-degree relatives of non-carriers.[7] The probability of cancer among the first-degree relatives of cases was calculated as the weighted mean likelihood that a relative is a mutation carrier multiplied by the probability of cancer according to mutation status. Penetrance was thus equal to twice the observed cancer incidence among the first-degree relatives of carriers, minus the observed cancer incidence among the first-degree relatives of non-carriers. If two cases were first-degree relatives of each other, their disease status was included, but none of their common relatives was included more than once. For example, if two sisters were diagnosed with cancer and were both included in our study, their mother was included only once, as were any other sisters they had. Sister 1, however, was included in the set of first-degree relatives of sister 2, and vice versa. The mutant allele frequency was set at 0·25%.[16,17] 95% CIs were calculated with a bootstrap method.[7] The cumulative incidence of breast cancer in each age group of first-degree relatives was estimated with Kaplan-Meier curves

Results

Mutation status for *BRCA2* was assessed for all 575 patients. Of the 541 women with breast cancer, 56 (10·4%) were positive for the 999del5 mutation in the *BRCA2* gene. 13 (38%) of the 34 men carried the mutation. The number of first-degree relatives of the study group (mutation carriers and non-carriers), and the numbers of cancers in those relatives, are shown in table 1. The estimated probabilities of disease for mutation carriers and non-carriers in each age-group are shown in the figure and table 2. The estimated risk of breast cancer was substantially higher for carriers of the 999del5 mutation than for non-carriers at age 50 and age 70 (table 2). The difference in risk between carriers and non-carriers was significant by age 34 ($p<0·05$). Among relatives of female patients only, the estimated risk of breast cancer was 15·4% (7·1–25·1) at age 50 and 35·4% (16·9–56·4) at age 70 (2·3% and 8·4%, respectively, for non-carriers). The risk of prostate cancer for men at age 70 was also higher for carriers than for non-carriers. The difference in prostate cancer risk between mutation carriers and non-carriers was marginally significant at age 63. Data on ovarian cancer were too sparse to allow us to draw any conclusion.

Discussion

We have estimated the risk of breast cancer among carriers of a *BRCA2* mutation in a series of 575 breast cancer patients and their first-degree female relatives. All 575 cancer patients were analysed for the founder mutation 999del5, present in around 0·6% of the Icelandic population, and 69 (12%) of the patients were carriers.

Our risk estimates are much lower than those of previous studies of high-risk pedigrees, which have

generally estimated the risk of cancer to be 80% or more by age 70 (compared with 37% in our study). Our estimate of a 37% risk of breast cancer at age 70 is also lower than the estimate of 56% from a community-based study of Ashkenazi Jews with *BRCA1/2* mutations. That study and ours estimated cancer risk from the cancer status of first-degree relatives of genotyped individuals, but without direct testing of the relatives. The study of Ashkenazi Jews was composed entirely of volunteers, and relied on their reports of cancer in relatives without verification. Since more volunteers reported a family history of breast cancer than would be expected for a truly representative sample, the estimated risk of cancer in that study is likely to be too high. We avoided this bias by sampling a representative population-based series of cases of breast cancer and by linking registry information with previously collected pedigree information. This process gave an accurate assessment of cancer occurrence in the close relatives of cases that were genotyped. Unless the probability that the *BRAC2* mutation will be transmitted is unequal for men and women, our methods of estimating risk of cancer penetrance should be unbiased, since around half of all the female first-degree relatives of mutation carriers should themselves be carriers.

There is some evidence that *BRCA2* mutations may have somewhat lower breast-cancer penetrance than *BRCA1* mutations in general,[7,21,22] and our results may partly reflect this. However, in the study of *BRCA1/2* mutations among the Ashkenazi Jews, the breast cancer penetrance for *BRCA2* mutations was 51%, only slightly lower than the overall estimate of 56%. The 999del5 mutation was originally found in a family at high risk of male breast cancer,[3,23] and subsequently in 15 other families with breast cancer.[16] This mutation leads to an early protein truncation, and loss of the normal allele is found in tumours. The Icelandic 999del5 mutation thus cannot be described as a low-risk mutation.

The incidence of breast cancer in Iceland has been increasing during the past 40 years, in parallel with other Western countries.[24,25] The observed variation in risk for carriers of the 999del5 mutation is consistent with the involvement of modifying factors, genetic or environmental, that affect risk for any given family or individual. A risk of breast cancer of 37% at age 70 is high and should be taken seriously. Counselling of patients about their risk of breast cancer should take account of family history.

Our results show that the mean risk of breast cancer for *BRCA2* mutation carriers is not as high as previously estimated. Iceland has both high-risk and low-risk *BRCA2* families, in a population with only one *BRCA2* mutation and an increasing overall incidence of breast cancer. Research is needed on possible interactions between genetic and environmental risk factors in the development of breast cancer.

Contributors

Jorunn Eyfjörd, Jeffery Struewing, and Steinunn Thorlacius designed the study, coordinated the work, and wrote the paper. Jorunn Eyfjörd and Steinunn Thorlacius did the mutation screening. Jeffery Struewing did the statistical analysis. Patricia Hartge proposed the study and participated in statistical analysis. Sholom Wacholder led the statistical analysis. Gudridur Olafsdottir managed the family data. Hrafn Tulinius, Head of the Cancer Registry, collected family data. Laufey Tryggvadottir contributed to epidemiological work, and Helgi Sigvaldason worked on statistical analysis. All investigators reviewed the paper.

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